CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 064150

BIOEQUIVALENCE REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

AADA 64-150

JUN 26 1996

Eon Labs Manufacturing Inc.
Attention: Yau-Kit Lam
227-15 North Conduit Avenue
Laurelton, NY 11413

Dear Mr. Lam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Rifampin Capsules, 300 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be incorporated into your manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of 0.1N HCl at 37°C using USP 23 apparatus 1 (basket) at 50 rpm. The test drug product should meet the following specifications:

   Not less than (b)4 of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

SEP - 5 1997

Rifampin
150 mg Capsule
NDA #64-150
Reviewer: J. Lee
64150DW.697

Eon Labs
Laurelton, NY
Submission date:
June 11, 1997

Review of Dissolution Data and a Request for Waiver

The sponsor has submitted a supplement to their approved application (app. 28 May 97) to include a new 150 mg strength in addition to the approved 300 mg capsule. An acceptable bio-study was conducted on the 300 mg capsule (S. Pradhan).

In support of the waiver request the company has submitted a formulation comparison between the approved 300 mg capsule and the proposed 150 mg capsule as well as comparative dissolution data between the 150 mg capsule vs Rifadin® 150 mg capsule (Merrell Dow Pharmaceuticals).

Comment:

1. The dissolution testing, using the current USP method (p. 2976) is acceptable.

Recommendation:

1. The dissolution testing conducted by Eon Labs, using the current USP method, on its rifampin 150 mg capsule, batch #960401, is acceptable.

2. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of 0.1N HCl at 37°C using USP XXIII apparatus I (100) at rpm. The test product should meet the following specification:

   Not less than (b)4 of the labeled amount of the drug in the capsule is dissolved in 45 minutes.

3. The Division of Bioequivalence agrees that the information submitted by the sponsor demonstrates that rifampin 150 mg capsule falls under 21 CFR 320.22 (d)(2) of Bioavailability/Bioequivalence Regulations. The Division of Bioequivalence recommends that the waiver of an in-vivo bioavailability study be granted. Eon's rifampin 150 mg capsule is deemed bioequivalent to Rifadin® 150 mg capsule manufactured by Merrell Dow Pharmaceuticals.

/S/ 9/19/97
J. Lee
Division of Bioequivalence

USP XXIII Apparatus __I__ Basket __x__ Paddle _____ rpm __100__

Medium: __0.1N HCl__ Volume: __900__ ml

Number of Tabs/Caps Tested: __12__

Reference Drug: __Rifadin® 150 mg capsule__

Assay Methodology: __UV absorbance @ 475 nm__

Results

Time (min)	Test Product Lot # 960401 Mean % Dissolved	Range	(CV)	Reference Product Lot # 4988AF Mean % Dissolved	Range	(CV)
15	97.1	(b)4 - Confidentia Business	(2.1)	89.8	(b)4 - Confidentia Business	(5.4)
30	97.3		(3.4)	96.5		(1.3)
45	97.9		(2.9)	97.1		(1.3)
60	98.7		(2.6)	97.7		(1.4)
____	_____	_____	( )	_____	_____	( )
____	_____	_____	( )	_____	_____	( )
	Lot #_____			Lot #_____		
____	_____	_____	( )	_____	_____	( )
____	_____	_____	( )	_____	_____	( )
____	_____	_____	( )	_____	_____	( )
____	_____	_____	( )	_____	_____	( )
____	_____	_____	( )	_____	_____	( )
____	_____	_____	( )	_____	_____	( )

AADA 64-150 Rifampin Capsules, USP, 300 mg
Supplemental Application - Rifampin Capsules, USP, 150 mg

COMPOSITION COMPARISON BETWEEN RIFAMPIN CAPSULES, USP, 300 MG AND RIFAMPIN CAPSULES, USP, 150 MG

	Amount per capsule in mg		% W/W	
Component	**Rifampin Capsules, USP, 300 mg**	**Rifampin Capsules, USP, 150 mg**	**Rifampin Capsules, USP, 300 mg**	**Rifampin Capsules, USP, 150 mg**
Rifampin, USP	300.0	150.0	68.6	62.5
Microcrystalline cellulose, NF	(b)4 - Confidential Business			
Corn Starch, NF				
Colloidal Silicon Dioxide, NF				
Docusate Sodium (b)4 odium Benzoate (b)4				
Talc, USP				
Magnesium Stearate, NF				
Net Capsule Fill Weight	360.0	180.0	82.4	75.0
#2 Gelatin Capsule, Medium Orange Opaque Cap, Medium Orange Opaque body, Imprinted "E 801" in Black	77.0 (± 6 mg)	60.0 (± 5 mg)	17.6	25.0
Total Filled Capsule Weight	437.0	240.0	100.0	100.0

Note: The amount of active and inactive ingredients of Rifampin Capsules, USP, 300 mg and 150 mg strengths are proportional, the amount of each ingredient for Rifampin Capsules, USP 150 mg represents half the amount of each corresponding ingredient for Rifampin capsules, USP, 300 mg. It should be noted, that the weight of the capsule shells for the 150 mg strength is not half the weight of the capsules shells for the 300 mg strength . 60 mg versus 77 mg respectively, consequently the %w/w composition is not proportional.

JUN 14 1996

Rifampin
300 mg Capsules
AADA # 64-150
Reviewer: Sikta Pradhan, Ph.D.
WP #64150ASD.D95

Eon Labs Manufacturing, Inc.
Laurelton, NY
Submission Date:
December 14, 1995

REVIEW OF AN AMENDMENT TO A BIOEQUIVALENCE STUDY

Introduction

Rifampin is a semisynthetic derivative of rifamycin B, an antibiotic produced by certain strains of Streptomyces mediterranei. Rifampin is used in the treatment of both tuberculosis and the meningococcal carrier state. It inhibits DNA-dependent RNA polymerase activity in susceptible cells. It interacts with bacterial RNA polymerase but does not inhibit the mammalian enzyme.

Rifampin is currently available as Rifadin^{R}, 150 mg and 300 mg capsules manufactured by Marion Merrell Dow. The usual daily dosage of rifampin is 600 mg to 1200 mg depending on the indication. The drug is usually administered 30 minutes to 1 hour before or 2 hours after food to ensure maximum absorption.

The firm had previously conducted a bioequivalence study on its test product. The objective of the study was to compare the relative bioavailability of Rifampin 300 mg capsules, manufactured by Eon Labs., Inc. with that of Rifadin^{R} 300 mg capsules, manufactured by Marion Merrell Dow, in healthy, male volunteers dosed under fasting condition.

This amendment contains the firm's responses to the reviewer's comments made on the submission dated April 12, 1995.

Agency's Comments:

1. (b)4 - Confidential Business

2.

(b)4 - Confidential Business

provided.

5. The firm should inform the Agency the Lot size of the test product used in the in vitro dissolution testing and in vivo bioequivalence study.

6. There were a number of blood collections that deviated from the target times due to late arrival of some subjects. The firm was requested to provide the reason for late arrival of each subject.

7. The firm was also requested to submit all statistical analyses conducted on the test and reference samples collected at each sampling time.

Firm's Responses:

The firm has responded the Agency's comments in this amendment and provided the following analytical information.

1.

2. (b)4 - Confidential Business

3.

4. [redacted]

(b)4 - Confidential Business

5. The Lot size of the test product used in the in vitro dissolution testing and in vivo bioequivalence study was [redacted](b)4 -[redacted]sules.

6. The firm has indicated that the reasons for the late arrival of subjects for scheduled blood draws were not recorded at the time. However, adjustments for these time deviations were made to the data set.

7. The firm has submitted the requested statistical analyses conducted on the test and reference samples collected at each sampling time. Statistical data were acceptable. There was no significant difference in plasma rifampin and 25-desacetyl rifampin levels produced by the test and reference products at any time except at 0.5 hour sampling time. At 0.5 hour, the plasma rifampin levels of the test and reference products was significantly different but the difference in 25-desacetyl rifampin levels was non-significant.

Approval Comments:

1. The firm's responses to the Agency's comments are acceptable, and therefore, the in vivo bioequivalence study under fasting condition on 300 mg Rifampin Capsules (lot # 941101) is acceptable.

2. The drug is usually administered 30 minutes to 1 hour before or 2 hours after food to ensure maximum absorption, and therefore, no in vivo bioequivalence study under fed condition on the test product is required.

3. The firm has conducted an acceptable in vitro dissolution testing on 300 mg Rifampin Capsules (lot # 941101).

4. An inspection of the study facilities and an audit of data have been requested through the Division of Scientific Investigations (HFD-340).

Recommendations:

1. The in vivo bioequivalence study conducted by Eon Labs Manufacturing Inc. on its 300 mg Rifampin Capsules of lot #941101, versus the reference product, Rifadin^{R} 300 mg Capsules manufactured by Marion Merrell Dow Inc. has been found to be acceptable to the Division of Bioequivalence. The study demonstrates that the test product, Rifampin Capsules is bioequivalent to the reference product, Rifadin^{R}, 300 mg capsule manufactured by Marion Merrell Dow Inc.

2. The in vitro dissolution testing conducted by Eon Labs Manufacturing, Inc. on its Rifampin 300 mg Capsules of lot #941101 is acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of 0.1N HCl at 37^{0}C using USP XXIII apparatus I (basket) at 50 rpm. The test drug product should meet the following specifications:

   Not less than (b)4 of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

/S/

Division of Bioequivalence
Review Branch I

RD INITIALED YCHUANG
FT INITIALED YCHUANG ---- /S/ 6/14/96

/S/

Concur: ----- Date: 6/14/96

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence

cc: ANDA # 64-150 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-344 (CViswanathan), HFD-652 (Huang, Pradhan), Drug File, Division File.

SP/06-13-96/X:\wpfile\Pradhan\64150ASD.D95 ~~96~~